Call for Comparative Effectiveness Research: Lowering A1c with Sitagliptin, Saxagliptin, or Cinnamon

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A flood of evidence-driven and largely unwelcome challenges to commonly accepted protocols for the treatment of type 2 diabetes prompted an editorialist to describe 2007-2008 as “an annus horribilis for research into type 2 diabetes management.” Speculation that thiazolidinediones (TZDs) would “more than fulfill their promise” to reduce rates of cardiovascular events in patients with type 2 diabetes was replaced by disappointment in May 2007, when Nissen and Wolski released a meta-analysis documenting an association between use of rosiglitazone and increased rates of myocardial infarction. Disappointment was heightened with the addition of black-box warnings for administration of TZDs to patients with congestive heart failure in August 2007 and for coadministration of rosiglitazone with insulin or nitrates in November 2007.

Treatment algorithms and guidelines were further pummeled when the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and Action to Control Cardiovascular Risk in Diabetes (ACCORD) randomized controlled trials found that intensive glucose control did not produce the hypothesized and hoped-for reduction in cardiovascular events but was instead associated with elevated rates of severe hypoglycemia and all-cause mortality. An additional shake-up in the diabetes drug market came in July 2008, when the Endocrinologic and Metabolic Drugs Advisory Committee of the U.S. Food and Drug Administration (FDA) recommended that assessments of the cardiovascular safety of new diabetes medications be required prior to FDA approval. The committee’s recommendation was adopted by the FDA in a “guidance for industry” document released in December 2008.

In the resulting wave of editorials about these developments, a commonly expressed concern was the effect of unexpected information on routine patient care. A key issue for some observers was that neither the patients nor the stringent hemoglobin A1c goals in the ACCORD and ADVANCE trials were representative of the more clinically and socioeconomically challenging situations faced by clinicians in routine practice, making it difficult to translate research findings into prescribing behavior. “Now what can a clinician possibly think?” asked one editorialist. Another editorialist argued that drug safety warnings for rosiglitazone would result in undertreatment of elevated A1c levels by practitioners already struggling to encourage patients to accept needed add-on therapy. Notably, that editorial was written in response to a commentary by Fanning et al. (2009), which included a brief report that among patients discontinuing rosiglitazone within 3 months after the publication of the Nissen and Wolski meta-analysis, 13% had no prescription claims for any oral antidiabetic agent in the 90-day period following the final rosiglitazone prescription.

Providing further insight into what actually happens following the delivery of unexpected news to the medical community, Starner et al. (2008) retrospectively analyzed administrative claims for 9 million members enrolled in 9 health plans, finding that use of rosiglitazone dropped by approximately 50% from April 2007 through December 2007, following 5 safety warnings regarding rosiglitazone. However, in May 2008, 12 months after publication of Nissen and Wolski’s findings, more than 20% of the remaining rosiglitazone users had clinical characteristics putting them at high cardiovascular risk, such as congestive heart failure, use of nitrates or insulin, or ischemic heart disease. Starner et al.’s findings highlight the conundrum facing many managed care organizations—the process of translating new information into routine clinical practice is nearly always difficult and sometimes slower than ideal.

New Developments from the FDA: Alogliptin Denied; Saxagliptin Approved

The pace of events faced by payers, providers, and manufacturers did not slow in 2009. In March 2009, the FDA advised the manufacturer of the dipeptidyl peptidase-4 (DPP-4) inhibitor alogliptin that its December 2007 new drug application (NDA) for once-daily treatment for patients with type 2 diabetes would be required to meet the cardiovascular safety data requirements promulgated in the December 2008 industry guidance. In June 2009, the FDA issued a complete response letter indicating that the available clinical data for alogliptin were insufficient to meet guidance requirements and requesting completion of a new cardiovascular safety trial. The trial, EXamination of CArdiovascular OutcoMes: AlogliptIN vs. Standard of CarE in Patients with Type 2 Diabetes Mellitus and Acute Coronary Syndrome (EXAMINE), will randomize approximately 5,400 patients in approximately 1,000 sites in the United States, Europe, and Asia. The primary outcome is time from randomization to occurrence of a major cardiovascular event, defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. Study completion is expected in December 2014. The trial is a high-stakes venture for alogliptin’s manufacturer, whose patent on pioglitazone, which generated 25% of the manufacturer’s revenue in 2008, expires in 2011.
Saxagliptin, another DPP-4 inhibitor for which an NDA had been filed in June 2008, took a different path than did aloglipsin, receiving FDA approval in July 2009 “as an adjunct to diet and exercise to improve glycemic control in adults” with type 2 diabetes. The FDA news release announcing approval of saxagliptin indicates that its NDA was submitted prior to the guidance requiring cardiovascular safety studies and that the drug was “not associated with an increased risk for cardiovascular events in patients who were mainly at low risk for these events” in the pivotal clinical trials. FDA approval was contingent upon the manufacturer’s agreement to complete a postmarketing randomized trial to assess the incidence of major adverse cardiovascular events. The study protocol is to be completed by November 2009, data collection by July 2015, and a final report by January 2016. The manufacturer will also be required to complete postmarketing studies of severe hepatic events and severe hypersensitivity and cutaneous reactions in patients treated with sitagliptin versus other antidiabetic medications.

New Development from Effectiveness Trial in Primary Care—Cinnamon Reduces A1c in Patients with Poorly Controlled Type 2 Diabetes

While the DPP-4 inhibitor pipeline is becoming increasingly crowded, with 19 products in development as of January 2008, some spice was added to the mix of treatments for type 2 diabetes with the publication in September 2009 of a small randomized controlled trial conducted by Crawford for adult patients of 3 primary care clinics at a U.S. military base. Crawford randomized 109 patients with type 2 diabetes and A1c greater than 7.0 to either usual care (n=54) or usual care plus 1 gram of cinnamon per day (500mg capsule twice daily, n=55). To meet the need for effectiveness trials in patients seen in routine clinical practice, Crawford imposed no sampling restrictions other than pregnancy, age younger than 18 years, or cinnamon allergy.

Patients in Crawford’s study had a clinical profile typical of poorly controlled type 2 diabetes. Mean (SD) body mass index (BMI, kilograms per squared meter) values were 31.9 (6.4) in the cinnamon-treated group and 32.9 (6.4) in the control group (P=0.38). Measured at baseline, the mean (SD) per patient numbers of diabetes medications were 1.76 (0.9) and 1.91 (0.9) in the treatment and control groups, respectively (P=0.39), and A1c values were similar at 8.47 (1.8) and 8.28 (1.3), respectively (P=0.54). The percentages of insulin-dependent patients did not significantly differ in the treatment and control groups (38.2% and 33.3%, respectively, P=0.46).

In intention-to-treat analysis at 90 days after randomization, A1c change was a mean –0.83 (95% confidence interval [CI] =0.46-1.20) in the cinnamon-treated group and –0.37 (95% CI=0.15-0.59) in the control group (P for between-group difference in change<0.04 by t-test). The mean number of diabetes drug dosage adjustments during the 90-day follow-up was 0.3 in both groups, and the mean (SD) numbers of diabetes medications at study end were 1.74 (0.9) and 2.02 (0.9) for the treatment and control groups, respectively (P=0.12). Of the 46 patients who completed cinnamon treatment, 42 (91.3%) reported taking at least 75% of the cinnamon capsules.

Crawford’s favorable results for cinnamon treatment are not consistent with the results of a smaller study conducted by Blevins et al. (2007), the only other randomized trial of the use of cinnamon in U.S. patients with type 2 diabetes. In the study by Blevins et al., change in A1c levels at 3 months after randomization did not significantly differ for patients receiving usual care plus placebo (n=28, A1c mean [SD] change = +0.1 [0.2]) versus usual care plus 1 gram cinnamon per day (500mg twice daily, n=29; +0.2 [0.1], P=0.64).

Comparison of the Crawford and Blevins et al. results is problematic; Crawford’s sample has better external validity for patients with poorly controlled diabetes in routine primary care. The most notable difference is that patients with insulin-dependent diabetes, who constituted 35.8% of Crawford’s sample, were excluded from the Blevins et al. study. Also excluded by Blevins et al. were patients with any adjustments, initiation, or discontinuation of any of the following medications during follow-up: sulfonylureas, meglitinides, metformin, TZDs, alpha-glucosidase inhibitors, exenatide, statins, ezetimibe, niacin, or fibrin acid derivatives. Thus, it is not surprising that baseline A1c levels in the Blevins et al. study were already relatively low and near A1c goal, means (SD) of 7.2 (0.3) and 7.1 (0.2) in the treatment and control groups, respectively.

Comparative Effectiveness Trial Needed: Cinnamon in Type 2 Diabetes

Crawford concludes that cinnamon supplementation should be considered in addition to usual care in patients with poorly controlled type 2 diabetes. The potential implications of his findings for future research and patient care are intriguing. The reduction in A1c achieved with cinnamon treatment in the Crawford study (placebo-adjusted A1c change = –0.46) is only slightly less than the placebo-adjusted reductions reported in the product labels (Table 1) for sitagliptin (–0.6 to –0.9; all 7 studies published) and saxagliptin (–0.4 to –0.8; none of the 4 studies published). The A1c findings reported by Crawford are more convincing than the Blevins et al. findings because the baseline A1c levels in Crawford’s study groups were similar to those in the clinical trials for sitagliptin and saxagliptin (i.e., A1c equal to or greater than 8.0%).

However, the findings reported by Crawford are not sufficient to suggest replacement of DPP-IV inhibitors or other oral antidiabetic drugs with cinnamon in routine patient care. Comparative research seems warranted to determine the head-to-head effectiveness of cinnamon versus sitagliptin and saxagliptin in routine primary care, with the results likely to be helpful to clinicians seeking new tools to combat type 2 diabetes.
The potential cost savings for patients and payers are impressive. Drug costs for 3 months of treatment with daily dosages of sitagliptin 100 mg and saxagliptin 2.5 mg or 5 mg are $556 and $520, respectively. In contrast, cinnamon 1 gram (two 500 mg capsules) daily costs less than $20 for a 3-month supply, meaning that 25-30 patients can be treated with cinnamon for 1 patient treated with sitagliptin or saxagliptin. Amid reported outcomes for newer antidiabetic drugs that include adverse effects revealed only in postmarketing experience and comparable efficacy but higher cost compared with older agents, Crawford’s findings are a refreshing change and seemingly more palatable for payers and patients.

### Table 1: A1c Change Results from Randomized Controlled Trials of Sitagliptin and Saxagliptin in Adult Patients with Type 2 Diabetes

<table>
<thead>
<tr>
<th>First Author and Year</th>
<th>Comparison</th>
<th>Treatment N</th>
<th>Control N</th>
<th>Length</th>
<th>Mean Baseline A1c</th>
<th>Mean Change in A1c</th>
<th>Mean (95% CI) Difference from Controla</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raz 200624</td>
<td>Sitagliptin 100 mg monotherapy vs. placebo</td>
<td>193</td>
<td>103</td>
<td>18 weeks</td>
<td>8.0</td>
<td>8.1</td>
<td>–0.5</td>
</tr>
<tr>
<td>Aschner 200623</td>
<td>Sitagliptin 100 mg monotherapy vs. placebo</td>
<td>229</td>
<td>244</td>
<td>24 weeks</td>
<td>8.0</td>
<td>8.0</td>
<td>–0.6</td>
</tr>
<tr>
<td>Charbonnel 200626</td>
<td>Sitagliptin 100 mg + metformin vs. placebo + metformin</td>
<td>453</td>
<td>224</td>
<td>24 weeks</td>
<td>8.0</td>
<td>8.0</td>
<td>–0.7</td>
</tr>
<tr>
<td>Rosenstock 200627</td>
<td>Sitagliptin 100 mg + pioglitazone vs. placebo + pioglitazone</td>
<td>163</td>
<td>174</td>
<td>24 weeks</td>
<td>8.1</td>
<td>8.0</td>
<td>–0.9</td>
</tr>
<tr>
<td>Hermansen 200728</td>
<td>Sitagliptin 100 mg + glimepride vs. placebo + glimepride</td>
<td>102</td>
<td>103</td>
<td>24 weeks</td>
<td>8.4</td>
<td>8.5</td>
<td>–0.3</td>
</tr>
<tr>
<td>Hermansen 200728</td>
<td>Sitagliptin 100 mg + glimepride + metformin vs. placebo + glimepride + metformin</td>
<td>115</td>
<td>105</td>
<td>24 weeks</td>
<td>8.3</td>
<td>8.3</td>
<td>–0.6</td>
</tr>
<tr>
<td>Goldstein 200729</td>
<td>Sitagliptin 100 mg vs. placebo</td>
<td>175</td>
<td>165</td>
<td>24 weeks</td>
<td>8.9</td>
<td>8.7</td>
<td>–0.7</td>
</tr>
</tbody>
</table>

a Placebo-controlled clinical trials reported in the product labels. One placebo-controlled study of saxagliptin, labeled as “Table 6” in the product label, is not included here because dosage adjustments to glyburide were permitted in the placebo group but not in the saxagliptin-treated groups.
b Represents difference between change in treatment group versus control group.
c Because none of the studies described in the saxagliptin product label could be located in the published literature, the product label was the sole source of information. All placebo-controlled studies that were reported in the sitagliptin product label were published.
CI = confidence interval; mg = milligrams; TZD = thiazolidinedione.
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DISCLOSURES

The authors report no conflicts of interest related to the subjects or products discussed in this article.

REFERENCES

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